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EXAMINER

BRANNOCK, MICHAEL T

ART UNIT

PAPER NUMBER

1646

DATE MAILED: 05/06/2003

13

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No. 09/848,664	Applicant(s) Sakiyama-Elbert et al.
Examiner Michael Brannock	Art Unit 1646



-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on Feb 10, 2003

2a) This action is FINAL. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

4) Claim(s) 1, 3-7, 20, 21, 24-27, 57, 58, and 61-65 is/are pending in the application.

4a) Of the above, claim(s) 21 is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 1, 3-7, 20, 24-27, 57, 58, and 61-65 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) All b) Some* c) None of:
1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).
a) The translation of the foreign language provisional application has been received.

15) Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) Notice of References Cited (PTO-892)

2) Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) Information Disclosure Statement(s) (PTO-1449) Paper No(s). 6

4) Interview Summary (PTO-413) Paper No(s). _____

5) Notice of Informal Patent Application (PTO-152)

6) Other: _____

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DETAILED ACTION

Status of Application: Claims and Amendments

1. Applicant is notified that the amendments put forth in Paper 8, 10/29/02, have been entered in full.
2. Applicant's election of Claims 1, 3-7, 20, 24-27, 57-59 and 61-65 in Paper No. 6, 2/28/2000 is acknowledged.

Claim 21 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species of invention, there being no allowable generic or linking claim. Although Applicant did not appear to traversed the restriction (election) requirement, Applicant is reminded that there is no allowable generic or linking claim. Therefore, the restriction requirement is maintained and made final.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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4. Claims 1, 3-7, 20, 21, 24-27, 57-59 and 61-65 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the following reasons:

As per claims 1 and 62, the claims require that the composition comprise heparin or a heparin-like polymer, and that the protein growth factor have a domain that binds heparin with low affinity. First, it is unclear if the growth factor is required to bind to heparin with low affinity or if it need only have a domain that binds with low affinity but may also have domains that bind with higher affinity. Thus, the artisan could not be sure that he or she was not practicing the claimed invention when using a growth factor that also contained a high affinity domain.

Second, it is unclear whether or not the growth factor is required to bind with low affinity to *the* heparin or heparin-like polymer that is used in the composition, or is the growth factor only required to bind with low affinity to a reference heparin that does not necessarily have to be the same heparin as is used in the composition. The terms "heparin" and "heparin-like" are generic terms that describe an essentially limitless number of heterogenous individual compounds. Each of which have unique binding properties with regard to a particular protein. Even what may appear to be very similar fractions of heparin may have widely divergent binding properties. The art recognizes that different sources of heparin can produce large differences in the measured binding to a particular protein, see Lee et al., PNAS 88(2768-2772)1991, last paragraph of page 2772. This phenomena is well established in the art and encompasses the binding of many different types of proteins to heparin and heparin-like molecules. For example, McCaffrey et al.,

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U.S. Patent No: 5807982, report that commercially available heparin can be separated into subfractions, some of which bind to the growth factor TGF- β with high affinity and some that bind with very low affinity (see Abstract). Thus, in order to be reasonably appraised of the metes and bounds of the claims, the artisan would need to know which heparin or heparin like molecules are to be in the composition and which are to be the reference heparin that demonstrates low affinity binding. Because the affinity of the growth factor for heparin is dependent on the identity of the heparin, and because of the lack of standards regarding what fractions of heparin bind to which growth factors, it appears that the only way that the artisan could be reasonably appraised of the metes and bounds of the claims would be for the claims to require that the heparin or heparin-like compound that is used in the composition be the same heparin that binds the growth factor with low affinity. Suggested claim language is below.

Additionally, claim 26 requires "a derivative thereof". This is a relative phrase and the specification has not set forth how to determine the degree of derivation encompassed by the claim nor how to determine when a compound is no longer to be considered to be a derivative. Thus the metes and bounds of the claim cannot reasonably be determined.

It is suggested to Applicant that the following claim language would be allowable:

A drug delivery composition comprising:

- a) a substrate;

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b) a peptide comprising a domain that binds heparin or heparin-like compounds with high affinity, wherein the peptide is covalently bound to the substrate so that the heparin binding domain is able to bind to heparin or heparin-like compounds;

c) heparin or a heparin-like polymer;

d) a protein growth factor or a peptide fragment thereof having a domain that binds heparin with low affinity, wherein the protein growth factor or a peptide fragment thereof binds with low affinity to the heparin or heparin-like polymer of (c), and wherein low affinity is defined as not binding with the heparin or heparin-like polymer of (c) at a NaCl concentration of between about 25 mM and 140 mM.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

6. Claims 1, 3-7, 20, 24-27, 57, 58, 61-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schroeder-Tefft, J.A. *et al.* *J. of Controlled Release* 48(29-33)1997 in view of Kwon G.S. *et al.*, *J. of Controlled Release* and DeBlois, C. *et al.*, *Biomaterials* 15:9(665-672)1992.

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Schroeder-Tefft, J.A. *et al.* disclose a matrix for growth factor delivery (see the Title), that is sterile (see page 30, 2.1 *Formulations*) and suitable for implantation (see page 32 3.4 *Growth factor in vivo activity*) comprising: a peptide (collagen, which is capable of supporting cell attachment see page 32, 3.4 *Growth factor in vivo activity*) comprising a binding domain that binds heparin (non-covalently, e.g. instant claim 64) with high affinity (see page 32, line 6), heparin, and a growth factor polypeptide having a domain that binds heparin with low affinity (TGF- β 2) (see the abstract, and page 13, line 26 of the instant specification). Additionally, Schroeder-Tefft, J.A. teach that other growth factors such as BMPs, FGFs, IGF, EGF and VGEF could be used as well, see the last paragraph of page 32, the use of vascular endothelial growth factor (VGEF) being obvious to use in a vascular graft (e.g. claim 57). Further, the molar ration of heparin to growth factor is at least one, i.e. 0.1 mg heparin/0.1 mg TGF- β 2, assuming a minimum molecular weight of 3000 Daltons for heparin (see page 30, 2.1 *Formulations*). Schroeder-Tefft, J.A. *et al.* do not disclose, specifically, a substrate capable of providing attachment of a heparin-binding polypeptide.

Kwon G.S. *et al.* disclose a matrix similar to that of Schroeder-Tefft, J.A. *et al.* and to the claimed invention; the difference being that the peptide that binds heparin with high affinity does so via covalent attachment of heparin to the polypeptide (see first paragraph of Methods) (see claim 56), and not via a high affinity binding domain. Kwon G.S. *et al.* teach that heparin based matrices are useful for the controlled release of polypeptides (see page 920, last paragraph) wherein the polypeptides are positively charged, i.e., having a basic isoelectric point (see page

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89, col 2, 2nd paragraph). DeBlois, C. *et al.* teach that fibrin is useful as a substrate capable of providing attachment to collagen, and to cells, in a heparin based controlled release matrix, which has numerous biomedical applications including vascular prostheses and skin graphs (see page 672, last paragraph). Also, DeBlois teach a substrate (collagen sponge) and a peptide (fibrin) which has heparin binding domains, to which heparin and growth factor are added (pg 666, col 2), to control the release of a growth factor.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made, and with reasonable expectation of success, to construct a heparin-based growth factor delivery matrix, wherein the heparin was non-covalently attached to a polypeptide (collagen) as taught by Schroeder-Tefft, J.A. *et al.* or covalently attached to polypeptide as taught by Kwon G.S. *et al.*, such matrix also containing a substrate (fibrin) providing attachment to collagen, and collagen -being capable of supporting cell attachment, for the purpose of producing vascular prosthesis as taught by DeBlois, C. *et al.*, wherein the growth factor, e.g. TGF β 2, has low affinity for heparin elutes from a heparin at an NaCl concentration between 25-140 mM (see page 13 bridging 14 of the instant specification). It comprises a length of 8-30 amino acids having at least 2 basic residues and has a basic to acidic residue ratio of at least 2, a ratio of hydrophobic residues to basic amino acids of at least 0.67, and it contains the amino acid sequence identified as SEQ ID NO: 6, further, the amino acid identities and residues in disulfide bond formation are inherent to the molecule. Additionally, the claimed limitations required of heparin and heparin-like polymers are properties inherent to the molecules, e.g. it is well known

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in the art that heparin is available having a molecular weight of 6000-30000 Daltons and having at least one negative charge per two saccharide rings and to not have positive charge. All of the claim elements are taught by the combination of Schroeder-Tefft, J.A. *et al*, Kwon G.S. *et al*. DeBlois, C. *et al*. Whether a particular component is thought of as a “substrate” or a “heparin binding peptide” appears to be mostly a question of semantics, e.g. fibrin can be called a “substrate” as in DeBlois, C. *et al*. (col 1., page 666) or collagen can be thought of as the substrate encapsulating the fibrin/heparin/growth factor matrix (e.g. Col 2, pg 666, Collagen-based sponges). Thus it would be a straight-forward and obvious matter of parameter optimization to construct and use the invention as claimed.

Applicant’s arguments in paper 8, 10/29/02, to the extent that the arguments relate to this rejection, are addressed below. Applicant argues that Schroeder-Tefft, J.A. *et al*. do not teach or suggest grafting a heparin to a collagen substrate. This argument has been fully considered but not deemed persuasive. DeBlois, C. *et al*. teach graphing a fibrin/heparin/growth factor matrix to a collagen substrate (e.g. Col 2, pg 666, Collagen-based sponges). Applicant’s additional arguments regarding the order of steps taught by Schroeder-Tefft, J.A. *et al*. are unpersuasive. Specifically, the examiner can find no evidence that binding of heparin to growth factor precludes the binding of heparin to collagen. If this were true, then it is difficult to understand why collagen would be used at all. The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate

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affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant. See MPEP § 2145 generally for case law pertinent to the consideration of applicant's rebuttal argument.

Additionally, Applicant argues that Schroeder-Tefft, J.A. *et al.* use heparin to stabilize the growth factor and not to release it. This argument has been fully considered but not deemed persuasive. One of skill in the art would appreciate that the authors of the Schroeder-Tefft article employed the affinity of the growth factor for heparin such that heparin, grafted to a collagen substrate, served as a docking and release site to provide delayed release (i.e. controlled release) of the growth factor (see the text of Schroeder-Tefft). See, also, item 8, below.

Applicant argues that the Kwon reference does not teach covalently binding a peptide to a substrate with heparin binding properties. This argument has been fully considered but not deemed persuasive. First, it is presumed that Applicant intended to state that it is the peptide that has heparin binding properties and not the substrate. Never-the-less, Kwon teaches covalently binding heparin to albumin whereas the instant invention discloses that a peptide that binds to heparin is covalently bound to a substrate. The teachings of Schroeder-Tefft in combination with those of Kwon provide one of ordinary skill with sufficient instruction to optimize the attachments of each of the components in such a way that is appropriate to the specific application of the drug delivery system - the attachment of the heparin binding peptide (e.g.

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collagen or albumin,) to the substrate being an obvious variant encompassed by the teachings of both Schroeder-Tefft and Kwon.

Applicant further argues that Kwon does not teach a peptide with heparin binding domains to help deliver a growth factor with a domain that binds with heparin with low affinity. This argument has been fully considered but not deemed persuasive. Kwon disclose a matrix similar to that of Schroeder-Tefft, J.A. and to the claimed invention; the difference being that the peptide that binds heparin with high affinity does so via covalent attachment of heparin to the polypeptide (see first paragraph of Methods) (see claim 56), and not via a high affinity binding domain. Kwon G.S. *et al.* (supra) teach that heparin based matrices are useful for the controlled release of polypeptides, but it is Schroeder-Tefft that teach the controlled release of a peptide that bind heparin with low affinity, e.g. TGF β 2.

Applicant argues that DeBlois, C. *et al.*, does not teach the delivery of growth factors that bind to heparin with low affinity. This argument has been fully considered but not deemed persuasive. First, it should be pointed out that the instant claims do not require that the growth factor bind to heparin with low affinity, only that the peptide have a domain that binds heparin with low affinity, see the rejection under 35 U.S.C. 112, second paragraph, above. The specification sets forth that growth factors that bind to heparin with high affinity do so via a characteristic domain (see page 1) as is well appreciated in the art. One of ordinary skill in the art would not expect that every part of the FGF molecule would bind to heparin with high affinity, thus the protein must have domains that do not bind with high affinity, absent evidence

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to the contrary. Second, it is Schroeder-Tefft that teach the controlled release of a peptide that is defined by the specification to bind to heparin with low affinity, e.g. TGF β 2, and also suggest the use of other growth factors, e.g. EGF, that are defined by the specification as binding to heparin with low affinity.

Additional References of Interest

7. The Merck Index (Merck & CO., Inc., Rahway, NJ, 1989) provides that heparin is defined as having a molecular weight of 6000-30000 Daltons and having at least one negative charge per two saccharide rings and to not have positive charge.(see page 4575, text and figure).
8. Hubbell, J.A. et al. *Current Opinion in Biotechnology* is considered relevant to the instant application, because the author, being one of skill in the art has provided a characterization of the Schroeder-Tefft article, referred to above, wherein Hubbell, J.A. et al. stated that the authors of the Schroeder-Tefft article employed the affinity of the growth factor for heparin such that heparin, grafted to a collagen substrate, served as a docking and release site to provide delayed release of the growth factor (see page 128, reference #20 of Hubbell et al.,)
9. Lyon et al., J. Biol. Chem 272(29)18000-18006, 1997 is considered relevant to the instant application because the authors characterize the binding of various TGF β growth factors to

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heparin and conclude that stocks of TGF β 2 bind with mixed affinity to heparin - the low affinity components probably representing denatured protein, see col 1 of page 18002.

Conclusions

10. 1, 3-7, 20, 24-27, 57, 58, 61-65 are not allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (703) 306-5876. The examiner can normally be reached on Mondays through Thursdays from 8:00 a.m. to 5:30 p.m.

The examiner can also normally be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, Ph.D., can be reached at (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MB

WY

May 4, 2003

Yvonne Eyler
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